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(54) Title: ANTIHYPERTENSIVE 5-[(IMIDAZO[4,5-b]PYRIDIN-3-YL)METHYL]BENZOFURAN DERIVATIVES

(57) Abstract

The invention relates to the compounds:
N-[2-[3-chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;
3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-methanol;
N-[2-[3-chloro-5-[[2-ethyl-5-[2-(hydroxypropyl)]-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;
3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-methanol;
N-[2-[3-chloro-5-[[5-[2-(hydroxypropyl)]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide; and physiologically acceptable salts and solvates thereof. The invention further relates to processes for their preparation, pharmaceutical compositions containing them, and to their use in medicine, particularly in the treatment of hypertension.

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ANTIHYPERTENSIVE 5-[(IMIDAZO[4,5-b]PYRIDIN-3-YL)METHYL]BENZOFURAN DERIVATIVES

This invention relates to benzofuran derivatives, processes for their preparation and pharmaceutical compositions containing them.

According to a first aspect of the invention there is provided a compound selected from:

N-[2-[3-chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;

3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl] methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-methanol;

N-[2-[3-chloro-5-[[2-ethyl-5-[2-(hydroxypropyl)]-7-methyl-3H-imidazo [4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;

3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl] methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-methanol;

N-[2-[3-chloro-5-[[5-[2-(hydroxypropyl)]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;
or a physiologically acceptable salt or solvate (e.g. hydrate) thereof.

The physiologically acceptable acid addition salts of the compounds of the present invention may be derived from inorganic or organic acids. Examples of such salts include hydrochlorides, hydrobromides, sulphates, phosphates, benzoates, methanesulphonates or trifluoroacetates.

The compounds may also form salts with suitable bases. Examples of such salts are alkali metal (e.g. sodium or potassium), alkaline earth metal (e.g. calcium or magnesium), ammonium and substituted ammonium (e.g. dimethylammonium, triethylammonium, 2-hydroxyethyldimethylammonium, piperazinium, N,N-dimethylpiperazinium, tetraethylammonium, piperidinium, ethylenediammonium and choline).

It will be appreciated that, for pharmaceutical use, the salts referred to above will be physiologically acceptable, but other salts may find use, for example in the preparation of the compounds of the present invention and the physiologically acceptable salts thereof.

According to a second aspect of the present invention we provide a compound of the present invention or a physiologically acceptable salt or solvate thereof for use in therapy.

In particular, the compounds of the present invention may be used in the treatment or prophylaxis of hypertension (for example, essential, malignant or resistant, caused by oral contraceptives, coarctation of the aorta or renal vascular disease) and pulmonary hypertension.

The compounds of the present invention may also be used in the treatment or prophylaxis of congestive heart failure, acute or chronic heart failure, aortic or cardiac insufficiency, post-myocardial infarction, renal insufficiency and renal failure (for example, as a result of diabetic nephropathy, glomerular nephritis, scleroderma or renal crisis), proteinuria, Bartter's syndrome, secondary hyperaldosteronism, Reynaud's syndrome, cerebrovascular insufficiency, peripheral vascular disease, diabetic retinopathy, glaucoma, atherogenesis and for the improvement of vascular compliance.

They are also potentially useful for the treatment of cognitive disorders such as dementia (e.g. Alzheimer's disease) and other CNS disorders, such as anxiety disorders, schizophrenia, depression and alcohol or drug (e.g. cocaine) dependency.

According to a further aspect of the present invention we provide a compound of the present invention or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned diseases, especially hypertension.

According to another aspect of the present invention we provide a compound of the present invention or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of the aforementioned diseases, especially hypertension.

According to a further aspect of the present invention we provide a method of treating the aforementioned diseases, especially hypertension, which method comprises administering an effective amount to a patient in need of such treatment of a compound of the present invention or a physiologically acceptable salt or solvate thereof.

It will be appreciated that the compounds of the present invention or a physiologically acceptable salt or solvate thereof may advantageously be used in conjunction with one or more other therapeutic agents, such as for example diuretics and/or different antihypertensive agents such as β-blockers, calcium channel blockers or ACE inhibitors. It is to be understood that such combination therapy constitutes a further aspect of the present invention.

It will be further appreciated that reference herein to treatment extends to prophylaxis as well as to the treatment and relief of established symptoms.

While it is possible that a compound of the present invention may be administered as the raw chemical it is preferable to present the active ingredient as a pharmaceutical formulation.

The compounds of the present invention and their physiologically acceptable salts and solvates may be formulated for administration in any convenient way, and the invention also includes within its scope pharmaceutical compositions comprising at least one compound of the present invention or a physiologically acceptable salt or solvate thereof adapted for use in human or veterinary medicine. Such compositions may be presented for use in a conventional manner in admixture with one or more physiologically acceptable carriers or excipients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Thus, the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation. Oral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients

such as binding agents, for example mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, microcrystalline cellulose or maize-starch; lubricants, for example, magnesium stearate or stearic acid; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup or carboxymethyl cellulose; emulsifying agents, for example, sorbitan mono-oleate; non-aqueous vehicles (which may include edible oils), for example, propylene glycol or ethyl alcohol; and preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The compounds or their salts or esters may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides. For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

It will be appreciated that both tablets and capsules may be manufactured in the form of sustained release formulations, such that they provide a controlled continuous release of the compounds according to the invention over a period of hours.

The compounds of the present invention and their physiologically acceptable salts and solvates may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g.

dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

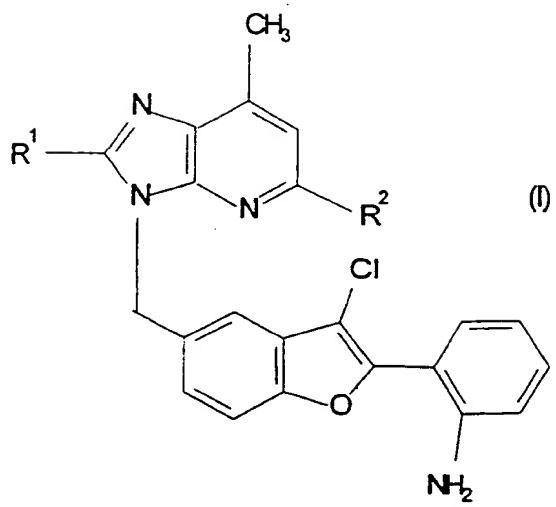
Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

The pharmaceutical formulations according to the invention may also contain other active ingredients such as antimicrobial agents, or preservatives.

It will be appreciated that the amount of a compound of the present invention required for use in treatment will vary not only with the particular compound selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will ultimately be at the discretion of the attendant physician or veterinarian. In general, however, when the compositions comprise dosage units, each unit will preferably contain 5mg to 500mg, advantageously where the compounds are to be administered orally 25mg to 400mg of the active compound. The daily dosage as employed for adult human treatment will preferably range from 5mg to 3g, most preferably from 25mg to lg which may be administered in l to 4 daily doses, preferably in 1 or 2 daily doses.

The compounds of the present invention may be prepared by a number of processes as described below.

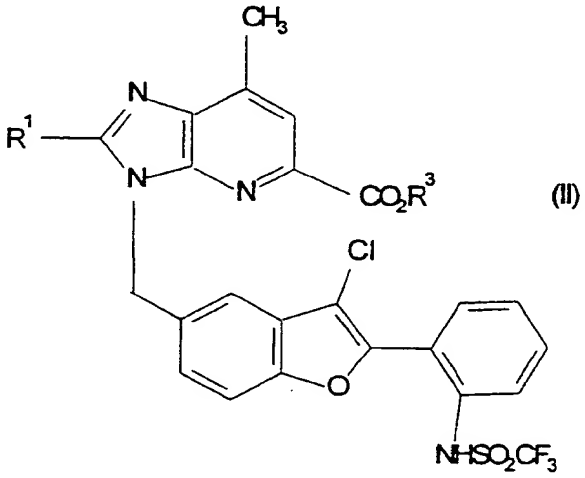
Thus, according to a further aspect of the present invention there is provided a process (A) for preparing the compounds of the present invention which comprises reacting a compound of formula (I)



(I)

(wherein R^1 is ethyl and R^2 is methyl) with trifluoromethanesulphonic anhydride or trifluoromethylsulphonyl chloride, in a suitable solvent such as a halogenated hydrocarbon, for example, dichloromethane or chloroform in the presence of a base, e.g. triethylamine.

In another process (B) compounds of the present invention may be prepared from a compound of formula (II)



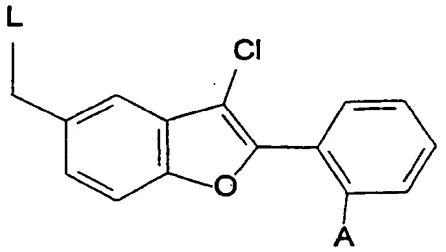
(II)

(wherein R^1 is ethyl or propyl and R^3 is a C_{1-4}alkyl group) by reduction (to convert the $-CO_2R^3$ group into $-CH_2OH$) using a reducing agent such as sodium borohydride or lithium aluminium hydride in a suitable solvent such as an alcohol (e.g. methanol or tert-butanol) or an ether (e.g. tetrahydrofuran) at any suitable temperature up to reflux; or by methylation (to convert the $-CO_2R^3$ group into

-$C(CH_3)_2OH$) using a Grignard reagent such as methyl magnesium bromide in an inert solvent such as an ether (e.g. tetrahydrofuran). The methylation reaction is completed by a hydrolysis step, using, for example a solution of ammonium chloride. The reaction is conveniently effected at a temperature between -78°C and the reflux temperature of the solvent.

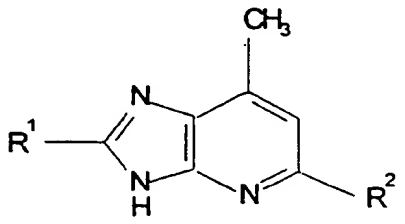
The intermediate compounds of formula (II) may be prepared from their corresponding amines by a triflamide formation according to the method of process (A). The corresponding amines may be prepared by methods analogous to those described herein below.

The intermediate compounds of formula (I) may be prepared by the alkylation of a compound of formula (III)



(III)

(wherein L is a leaving group, for example a halogen atom such as chlorine, bromine or iodine, or an alkyl- or arylsulphonyloxy group such as methanesulphonyloxy or p-toluenesulphonyloxy, and A is a protected amine group, for example, in the form of a carbamate using a tert-butoxycarbonyl (t-BOC) protecting group) with a suitable imidazopyridine compound of formula (IV)



(IV)

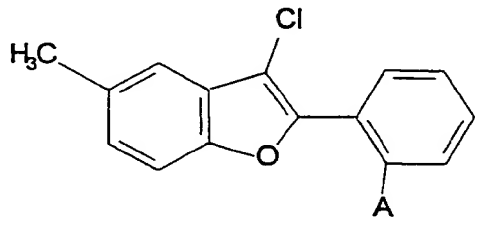
(wherein R^1 is ethyl and R^2 is methyl) followed by deprotection of the amine group. The alkylation reaction is preferably effected under basic conditions, for example, in the presence of sodium hydride, potassium carbonate or sodium

methoxide. The reaction is conveniently effected in a solvent such as acetonitrile or an ether e.g. tetrahydrofuran or dioxan, a ketone e.g. butanone or methyl isobutyl ketone, or a substituted amide e.g. dimethylformamide, at a temperature between 0°C and the reflux temperature of the solvent.

Deprotection of the amine group may be effected using techniques well known in the art, for example, by acid hydrolysis using trifluoroacetic acid in a suitable solvent such as a dichloromethane, conveniently at room temperature.

Alternatively, intermediate compounds of formula (I) may be prepared by reduction of the corresponding nitro compound using standard reducing conditions, for example, hydrogenolysis in the presence of a metal catalyst such as palladium or an oxide thereof on a support such as charcoal in a solvent such as an ether (e.g. tetrahydrofuran) and conveniently at room temperature and pressure.

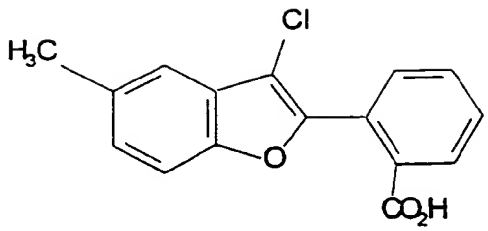
Compounds of formula (III) may be prepared from a compound of formula (V)



(V)

using any suitable reagent well known in the art for converting the methyl at the 5-position on the benzofuran ring into the group $-CH_2L$ (wherein L is as defined above). Thus, for example, when L is a halogen atom, a compound of formula (V) can be converted into a compound of formula (III) using N-chloro amides, tert-butyl hypochlorite or N-bromosuccinimide. Halogenation of the side chain may be catalysed by light, thus the reaction can be illuminated with a suitable artificial light source, and preferably in the presence of a free radical initiator such as azobisisobutyronitrile (AIBN) or benzoyl peroxide.

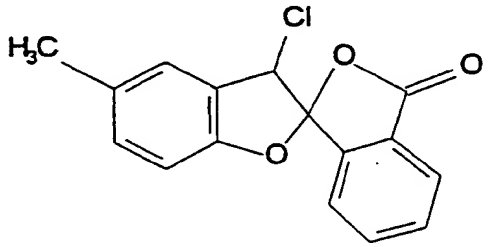
Compounds of formula (V) may be prepared by a Curtius rearrangement of the compound of formula (VI)



(M)

using, for example, diphenylphosphorylazide in the presence of a base such as triethylamine and in a solvent such as an alcohol (e.g. tert-butanol).

The compound of formula (VI) may be prepared from the corresponding des-chloro compound by a two step reaction. Firstly, 2-(5-methyl-2-benzofuranyl)benzoic acid is treated with a chlorinating agent such as N-chlorosuccinimide to give the intermediate of formula (VII)



(MI)

The chlorolactone of formula (VII) is then rearranged in the presence of a catalyst such as diazabicyclo[4.5.0]undec-7-ene (DBU) to give the compound of formula (VI).

Intermediates of formula (IV) may be prepared according to the methods described in European Patent Specification No. 0 400 974-A, published 5th December 1990.

The following examples illustrate the invention. Temperatures are in ^{0}C. "Dried" refers to drying using magnesium sulphate. Thin layer chromatography (t.l.c.) was carried out over silica and column chromatography was carried out on silica (Merck 9385 unless otherwise stated), using one of the following solvent systems : A - ether:hexane, B - ether:petroleum ether, C - dichloromethane:ethanol:ammonia, D-dichloromethane:ether, E - ethyl acetate:acetic acid, F - ethyl acetate:hexane, G - dichloromethane:methanol, H - dichloromethane:hexane, or I- methanol:ethyl

acetate, or J- ethyl acetate:hexan:acetic acid.

The following abbreviations are used : THF - tetrahydrofuran; DME - dimethoxyethane; DMF - dimethylformamide.

Intermediate 1
5-Methylbenzofuran-2-boronic acid
n-Butyl lithium (1.7M, 35.16ml) was added dropwise to a stirred solution of TMEDA (9.58ml) and 5-methylbenzofuran (8.22g) in ether (250ml) maintaining the temperature below - 60^{0}C throughout. The solution was warmed to about -10^{0}C over 45 minutes and stirred at this temperature for 30 minutes. A precipitate formed on warming. The suspension was cooled and triisopropylborate (43ml) was added, maintaining the temperature below -60^{0}C. The solution was warmed gradually to room temperature before quenching with 2N HCl (70ml). The mixture was extracted with ether (3x50ml) and the combined organic extracts washed with 2N HCl (4x30ml), water (2x30ml) and dried before evaporation to give the title compound as an orange solid (12.75g).
T.l.c. System A (1:1), Rf 0.3.

Intermediate 2
2-(5-Methyl-2-benzofuranyl)benzonitrile
Intermediate 1 (20g) was added to a stirred solution of 2- bromobenzonitrile (10.34g) and tetrakis(triphenylphosphine)palladium (0) (1.5g) in DME (200ml) and 8% $NaHCO_3$ (50ml) at reflux under nitrogen. Further catalyst (1.5g) was added and the reaction continued overnight. The reaction was cooled to room temperature and diluted with ether (200ml). The organic layer was separated, washed with water (3x100ml) and dried. Filtration and evaporation gave a white solid which was purified by chromatography eluting with System A (1:9) to give the title compound (10.58g) as a white solid.
T.l.c. System A (1:9), Rf 0.45.

Intermediate 2 was also prepared by the alternative two-step reaction:

a) 2-Hydroxy-5-methylbenzaldehyde
p-Cresol (100g) in dry THF(100ml) was added dropwise to a mechanically stirred, freshly prepared solution of ethyl magnesium bromide [magnesium (25.0g) and

bromoethane (75ml)] in THF (500ml) under nitrogen at a rate which maintained a slow reflux (about 30mins). After 30mins toluene (1.21) was added, followed by 1,3- dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (125ml), and paraformaldehyde (70g). The mixture was then heated at reflux for 16h. The mixture was concentrated by distillation and aqueous hydrochloric acid (2M, 600ml) then added. Water (600ml) was added and the mixture filtered through "hyflo". The organic phase was separated, dried, filtered and concentrated in vacuo to give a brown oil. The oil was steam distilled and the product extracted from the distillate with ether (1 litre). The organic extract was dried, filtered and concentrated in vacuo to give a pale yellow slurry which was cooled to -10^{0}C, triturated with ether (precooled to -78^{0}C, 100ml), filtered off rapidly and washed with ether (precooled to -78^{0}C) to give the title compound as colourless needles, (131.4g).
T.l.c. System A (1:5) Rf 0.5.

b) 2-(5-Methyl-2-benzofuranyl)benzonitrile
A solution of the product of step (a) (130g) in dry DMF (400ml) was added dropwise to a solution of sodium methoxide (56.2g) in ethanol (400ml) mechanically stirred under nitrogen. After 20mins, a solution of 2-(bromomethyl)benzonitrile (182.2g) in dry DMF (400ml) was added dropwise. The mixture was then heated to 75^{0}C for 30min. The solution was allowed to cool for 1h. A slurry of sodium methoxide (56.2g) in dry DMF (100ml) was added and the mixture heated at reflux for 1.5h. The mixture was concentrated in vacuo and then poured into iced water. The solid was collected, and then triturated with methanol to give the title compound (Intermediate 2) as a beige solid (149.4g).
T.l.c. System A (1:9) Rf 0.4.

Intermediate 3
2-(5-Methyl-2-benzofuranyl)benzoic acid
Intermediate 2 (10.0g) was suspended in glycerol and heated to 120^{o}C under an atmosphere of nitrogen. Solid potassium hydroxide (12.0g) was added, in portions, and the reaction mixture was heated to 170^{o}C. After 3 hours the mixture was cooled and poured into water (200ml). 2M hydrochloric acid (100ml) was added dropwise, with stirring, to the solution. The resulting yellowish solid was isolated by filtration and dried in vacuo to afford the title compound (12.05g).
T.l.c. hexane:ethyl acetate:acetic acid (15:5:1) Rf = 0.43

Intermediate 4

(±)-3-Chloro-5-methylspiro[benzofuran-2(3H),1' (3' H)-isobenzofuran]-3'-one

Intermediate 3 (11.95g) was dissolved in 1,4-dioxane (300ml) and water (4ml) was added. The mixture was placed under an atmosphere of nitrogen. N-chlorosuccinimide (7.67g) was added to the stirred solution which was then heated at reflux for 1.5 hours. The mixture was cooled to room temperature, diluted with ethyl acetate (300ml) and washed with brine (3x300ml). The organic solution was concentrated in vacuo to afford a solid (20.2g) which was triturated with methanol (350ml) and filtered to give the title compound (7.22g) as a white solid.

T.l.c. System F (1:3) Rf =0.49.

Intermediate 5

2-(3-Chloro-5-methyl-2-benzofuranyl)benzoic acid

Intermediate 4 (7.135g) was suspended in toluene (250ml) and 1,8-diazabicyclo[5.4.0]undec-7-ene (4.58g) was added slowly over a five minute period. The suspension was warmed to 45°C and stirred for 3 hours. The solution was then heated at reflux for 1 hour. The reaction mixture was cooled, diluted with toluene (500ml) and shaken with hydrochloric acid (250ml) and brine (250ml). The organic layer was dried and concentrated in vacuo to afford the title compound (6.78g) as a yellow solid.

T.l.c. hexane:ethyl acetate:acetic acid (15:5:1) Rf = 0.50

Intermediate 6

1,1-Dimethylethyl [2-[3-Chloro-5-methyl-2-benzofuranyl]phenyl]carbamate

Diphenylphosphoryl azide (41.5ml) was added dropwise to a stirred solution of Intermediate 5 (46.8g), triethylamine (23.55ml) and tert-butanol (30ml) in 1,4-dioxan (1400ml). The reaction mixture was heated at reflux overnight under a nitrogen atmosphere before being cooled and concentrated in vacuo to afford a brown residue (126g). Purification by column chromatography afforded the title compound (40.34g) as a white solid.

T.l.c. System A (1:20) Rf 0.29.

Intermediate 7

1,1-Dimethylethyl [2-[5-(bromomethyl)-3-chloro-2-benzofuranyl]phenyl]carbamate

Benzoyl peroxide (1.4g) was added to a stirred solution of Intermediate 6 (40.3g)

and N-bromosuccinimide (22.05g) in carbon tetrachloride (650ml). The suspension was heated at reflux for 2h, a light source (250 Watts) was applied and the mixture heated at reflux for a further 5h. The mixture was cooled, diluted with dichloromethane (900ml), washed with water (3x600ml), dried and concentrated in vacuo to afford the title compound (54g) as a solid.
T.l.c. System A (2:3) Rf = 0.75

Intermediate 8
Ethyl 2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
Hydrogen peroxide (30% w/w in water; 14ml) was added dropwise to stirred and cooled (-10°C) ethyl pyruvate (22ml). This mixture and a solution of iron (II) sulphate heptahydrate (37.5g) in water (45ml) were added simultaneously, dropwise into a stirred and cooled (-10°C) solution of 2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine (7.1g) in water (23ml) and concentrated sulphuric acid (7.5ml). The mixture was then poured onto ice and trisodium citrate dihydrate (40g) was added. The mixture was neutralised with solid sodium bicarbonate and partitioned between chloroform (x3) and water. The organic phases were combined, dried and evaporated. Column chromatography eluting with 10% methanol in ether gave a brown solid which was triturated with ether to give the title compound as a pale yellow solid (1.9g), m.p. 151-153°C.

Similarly prepared was:

Intermediate 9
Ethyl 7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
T.l.c. System G Rf = 0.43
From 7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine.

Intermediate 10
Ethyl 3-[[3-chloro-2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]phenyl]-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
A mixture of Intermediate 8 (13.0g) and potassium carbonate (8.56g) in anhydrous DMF (450ml) were stirred at room temperature with Intermediate 7 (32.0g) under nitrogen for 28 hours. The mixture was partitioned between aqueous sodium chloride solution (250ml) and extracted with ethyl acetate (3x300ml). The combined organic extracts were washed with 10% aqueous lithium chloride

solution (3x250ml), dried and the solvent removed in vacuo to give a yellow gum. This was purified by column chromatography eluting with System A (3:1) changing to ether only to give the title compound as a pale yellow foam (17.96g).
T.l.c. System A (2:1) Rf = 0.12

Similarly prepared was:-

Intermediate 11
Ethyl 3-[[3-chloro-2-[2-[[(1,1-dimethylethoxy)carbonyl]amino]pheny]-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
T.l.c. ether Rf = 0.3
From Intermediate 9 and Intermediate 7.

Intermediate 12
1,1-dimethylethyl [2-[3-chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]phenyl]carbamate
Sodium hydride (80% dispersion, 0.2g) was added over 5 mins to a solution of 5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (1g) in DMF (25ml) under a nitrogen atmosphere. After 30 mins, the solution was cooled to 0° and Intermediate 7 (4.23g) was added portionwise over 5 mins. The mixture was allowed to warm to room temperature and stirring continued overnight. The mixture was partitioned between water (50ml) and ethyl acetate (25ml) and the separated organic phase was washed with water:brine (1:1) (3x30ml), dried and concentrated in vacuo to give a brown oil (4.3g). Purification by chromatography eluting with System D (10:1) increasing to (5:1) afforded the title compound (1.34g) as a colourless foam.
T.l.c. System D (10:1) Rf 0.2

Intermediate 13
Ethyl 3-[[3-chloro-2-(2-aminophenyl)-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
Intermediate 10 (178.g) in dry dichloromethane (150ml) was treated dropwise with trifluoroacetic acid (50ml) and stirred under nitrogen at room temperature for 4 hours. The solution was concentrated in vacuo, diluted with ethyl acetate (200ml) and washed with 8% sodium bicarbonate solution. The combined aqueous extracts were then extracted with further ethyl acetate (100ml), the organic layer washed with further 8% sodium bicarbonate solution and then dried. The solvent

was removed in vacuo to give a brown solid which was triturated with ether to give the title compound as an off-white solid (13.72g).
T.l.c. ether Rf = 0.13

Similarly prepared were:-

Intermediate 14
Ethyl 3-[[3-chloro-2-(2-aminophenyl)-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
T.l.c. ether Rf = 0.2
From Intermediate 11.

Intermediate 15
2-[3-Chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]benzenamine
T.l.c. ether Rf = 0.39
From Intermediate 12.

Intermediate 16
Ethyl 3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
Trifluoromethanesulphonic anhydride (1M in dichloromethane; 15.76ml) was added dropwise to a solution of Intermediate 13 (7.0g) and triethylamine (2.4ml) in dry dichloromethane (100ml) at -65°C under nitrogen. After stirring for 1.5h, water (50ml) was added and the mixture stirred at room temperature for 20 mins. Ethyl acetate (20ml) and brine (100ml) were added and the aqueous layer acidified (to pH 6-7) and extracted with further ethyl acetate (2x100ml). The combined organic extracts were dried and the solvent removed in vacuo to give a foam. This was purified by column chromatography (alumina, Grade III) eluting with ethyl acetate changing to System E (9:1). Subsequent trituration with ether gave the title compound as a white solid (1.02g).
T.l.c. ethyl acetate Rf = 0.53

Similarly prepared was:-

Intermediate 17

Ethyl 3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-carboxylate
m.p. 89-92°C.
From Intermediate 14.

Example 1
N-[2-[3-Chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]phenyl]trifluoromethanesuphonamide
From Intermediate 15 according to the method of Intermediate 16.
T.l.c. ether Rf = 0.46
Assay Found: C,54.7; H,4.0; N,9.3;
$C_{26}H_{22}ClF_3N_4O_3S.0.5CH_3CO_2H$ requires: C,54.7; H,4.1; N,9.45%

Example 2
3-[[3-Chloro-2-[2-[[(trifluoromethyl)suphonyl]amino]phenyl]-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-methanol
Sodium borohydride (0.349g) was added to a stirred suspension of Intermediate 15 (1.911g) in tert-butanol (50ml). The mixture was heated to reflux for 15 mins and the methanol (3.5ml) was carefully added dropwise. The mixture was stirred at reflux for 2 hours. The cooled mixture was poured into dilute brine (100ml) and extracted with ethyl acetate (2x80ml). The combined organic extracts were dried and concentrated in vacuo to give a white foam. Purification by column chromatography eluting with System F (2:1) changing to System E (200:1) followed by trituration in System A gave the title compound as a white solid (922mg).
T.l.c. ethyl acetate Rf = 0.31
n.m.r. ($CDCl_3$, 250MHz) δ 1.35 (t,3H), 2.68 (s,3H), 2,85 (q,2H), 4.82 (s,2H), 5.6 (s,2H), 6.96 (s,1H), 7.2 (dd,1H), 7.4-7.6 (m,4H), 7.68 (dd,1H), 7.83 (dd,1H).

Similarly prepared was:

Example 3
3-[[3-Chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-methanol
T.l.c ethyl acetate Rf = 0.4
m.p. 119-124°C

From Intermediate 17.

Example 4

N-[2-[3-Chloro-5-[[2-ethyl-5-[2-(hydroxypropyl)]-7-methyl-3H-imidazo [4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide

Methyl magnesium bromide (15M solution in THF/toluene; 13.3ml) was added dropwise to a stirred solution of Intermediate 16 (2.90g) in dry THF (50ml) at 0° and the mixture stirred for 2 hours. Water (150ml) was added cautiously and the resultant mixture acidified to pH5-6 with dilute hydrochloric acid. The mixture was extracted with ethyl acetate (3x175ml). The combined extracts were washed with saturated brine (100ml), dried and concentrated in vacuo to give a brown oil. Purification by column chromatography eluting with System F (2:1) changing to system E (99:1) followed by trituration in System A gave the title compound as a white solid (1.21g).

T.l.c. ethyl acetate Rf = 0.5

n.m.r. (DMSO, 400MHz) δ 1.32 (t,3H), 1.58 (s,6H), 2.6 (s,3H), 3.06-3.14 (br.q, 2H), 5.7 (s,2H), 7.2 (br.s, 1H), 7.4-7.6 (m,6H), 7.8 (s,1H).

Similarly prepared was:

Example 5

N-[2-[3-Chloro-5-[[5-[2-(hydroxypropyl)]-7-methyl-2-propyl-3H-imidazo[4,5-b] pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide

T.l.c. ethyl acetate Rf 0.5

Assay Found: C,56.3; H,4.6; N,8.7;

$C_{29}H_{28}ClF_3N_4O_4S$ requires: C,56.1; H,4.5; N,9.0%

From Intermediate 17.

The compounds of the invention are tested in vitro for angiotensin II receptor antagonism. Aortic strips are obtained from male New Zealand white rabbits and prepared for recording isometric contractions in response to cumulative addition of angiotensin II. The potencies of test antagonists are assessed by measuring their abilities to displace the angiotensin II cumulative concentration response curve. The method used is that of Ackerly et al., Proc. Natl. Acad. Sci., 74(12), pp5725-28 (1977) with the exception that the final composition of the physiological salt solution is as given below in the Table:

Table 1	
Ingredient	Amount (mM)
Na^+	143.4
K^+	5.9
Mg^{2+}	0.6
Ca^{2+}	1.3
Cl^-	124.5
HPO_4^-	1.2
SO_4^{2-}	0.6
HCO_3^-	25.000
glucose	11.1
indomethacin	0.005
ascorbic acid	0.1

The tissues are initially challenged with K^+ (80mM) and then washed at 0, 5, 10 and 15 minutes after the response to K^+ has plateaued. After a further 45 minutes an angiotensin II cumulative response curve is constructed (0.1nM to 0.1μM in 10-fold increments) and the tissues are washed as before. A second, third and fourth angiotensin II cumulative response curve (0.1nM to 0.1μM in 3-fold increments) is then constructed at hourly intervals (15 minutes washing after each curve followed by 45 minutes equilibration). The compounds of the invention (30μM) are tested for angiotensin II receptor antagonism by application 45 minutes before construction of the fourth angiotensin II curve. The third and fourth angiotensin II curves are expressed graphically and a concentration ratio (CR) is calculated by dividing the angiotensin II EC_{50} value obtained in the presence of the test antagonist (i.e. fourth curve) by the angiotensin II EC_{50} value obtained in the absence of the test antagonist (i.e. third curve).

The potency of the test antagonist is expressed as a pKb which is calculated from the equation:

$$pKb = -\log \left[\frac{CR\text{-}1}{[antagonist]} \right]$$

which is a rearrangement of equation 4 described by Furchgott, in Handbook of Exp. Pharmacol., 33, p290 (1972) (eds. Blaschko and Muscholl).

If a compound supresses the maximum response to angiotensin II, a pKb is estimated using the double reciprocal plot technique for insurmountable antagonists, described by T.P. Kenakin, Pharmacol. Rev., 36(3), pp165-222 (esp. 203-204) (1984).

Thus, for example, the following data have been generated for compounds of the present invention. Where suppression was observed, the pKb has been estimated as discussed above.

Example No.	pKb
1	8.2
2	8.7 (estimated)
3	8.9 (estimated)
4	8.6 (estimated)
5	8.9 (estimated)

The compounds of the present invention have been found to induce a sustained reduction in blood pressure following oral administration to renal artery ligated hypertensive rats (Hilditch et al, Br. J. Pharmacol., 104, 423P (1991)). Thus we have found that the compounds of the invention inhibit the action of the hormone angiotensin II and are therefore useful in the treatment of conditions in which it is desirable to inhibit angiotensin II activity.

There is thus provided as a further aspect of the present invention a compound of the present invention or a physiologically acceptable salt or solvate thereof for use in the treatment of conditions associated with excessive or unregulated

angiotensin II activity.

In a further or alternative aspect of the invention there is provided a compound of the present invention or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of conditions associated with excessive or unregulated angiotensin II activity.

There is also provided in a further or alternative aspect of the invention a method for the treatment of conditions associated with excessive or unregulated angiotensin II activity in a mammal including man comprising administration of an effective amount to a mammal in need of such treatment a compound of the present invention or a physiologically acceptable salt or solvate thereof.

In addition, by virtue of their antagonistic activity at angiotensin II receptors, compounds of the present invention will be of value in the treatment of conditions associated with activation of the Renin-Angiotensin System.

There is thus provided a further aspect of the present invention a compound of the present invention or a physiologically acceptable salt or solvate thereof for use in the treatment of a condition associated with activation of the Renin-Angiotensin system.

In a further or alternative aspect of the present invention there is provided a compound of the present invention or a physiologically acceptable salt or solvate thereof for the manufacture of a therapeutic agent for the treatment of a condition associated with activation of the Renin-Angiotensin System.

There is also provided in a further or alternative aspect of the present invention a method for the treatment of a condition associated with the activation of the Renin-Angiotensin System in a mammal including man comprising administration of an effective amount to a mammal in need of such treatment of a compound of the present invention or a physiologically acceptable salt or solvate thereof.

The following examples illustrate pharmaceutical formulations according to the invention. The term "active ingredient" is used herein to represent a compound of

the present invention.

Pharmaceutical Example 1

Oral Tablet A

Active Ingredient	700mg
Sodium starch glycollate	10mg
Microcrystalline cellulose	50mg
Magnesium stearate	4mg

Sieve the active ingredient and microcrystalline cellulose through a 40 mesh screen and blend in an appropriate blender. Sieve the sodium starch glycollate and magnesium stearate through a 60 mesh screen, add to the powder blend and blend until homogeneous. Compress with appropriate punches in an automatic tablet press. The tablets may be coated with a thin polymer coat applied by the film coating techniques well known to those skilled in the art. Pigments may be incorporated in the film coat.

Pharmaceutical Example 2

Oral Tablet B

Active Ingredient	500mg
Lactose	100mg
Maize Starch	50mg
Polyvinyl pyrrolidone	3mg
Sodium starch glycollate	10mg
Magnesium stearate	4mg
Tablet Weight	667mg

Sieve the active ingredient, lactose and maize starch through a 40 mesh screen and blend the powders in a suitable blender. Make an aqueous solution of the polyvinyl pyrrolidone (5 - 10% w/v). Add this solution to the blended powders and mix until granulated; pass the granulate through a 12 mesh screen and dry the granules in a suitable oven or fluid bed dryer. Sieve the remaining components through a 60 mesh screen and blend them with the dried granules. Compress, using appropriate punches, on an automatic tablet press.

The tablets may be coated with a thin polymer coat applied by film coating techniques well known to those skilled in art. Pigments may be incorporated in the film coat.

Pharmaceutical Example 3

Inhalation Cartridge	
Active Ingredient	1mg
Lactose	24mg

Blend active ingredient, particle size reduced to a very fine particle size (weight mean diameter ca. 5µm) with the lactose in a suitable powder blender and fill the powder blender into No. 3 hard gelatin capsules.

The contents of the cartridges may be administered using a powder inhaler.

Pharmaceutical Example 4

Injection Formulation	% w/v
Active ingredient	1.00
Water for injections B.P. to	100.00

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the active ingredient using dilute acid or alkali or by the addition of suitable buffer salts. Antioxidants and metal chelating salts may also be included.

The solution is prepared, clarified and filled into appropriate sized ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen.

CLAIMS:

1. A compound selected from:
N-[2-[3-chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;

3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-methanol;

N-[2-[3-chloro-5-[[2-ethyl-5-[2-(hydroxypropyl)]-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;

3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-methanol;

N-[2-[3-chloro-5-[[5-[2-(hydroxypropyl)]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;
or a physiologically acceptable salt or solvate thereof.

2. The compound
N-[2-[3-chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;
or a physiologically acceptable salt or solvate thereof.

3. The compound
3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-2-ethyl-7-methyl-3H-imidazo[4,5-b]pyridine-5-methanol;
or a physiologically acceptable salt or solvate thereof.

4. The compound
N-[2-[3-chloro-5-[[2-ethyl-5-[2-(hydroxypropyl)]-7-methyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;
or a physiologically acceptable salt or solvate thereof.

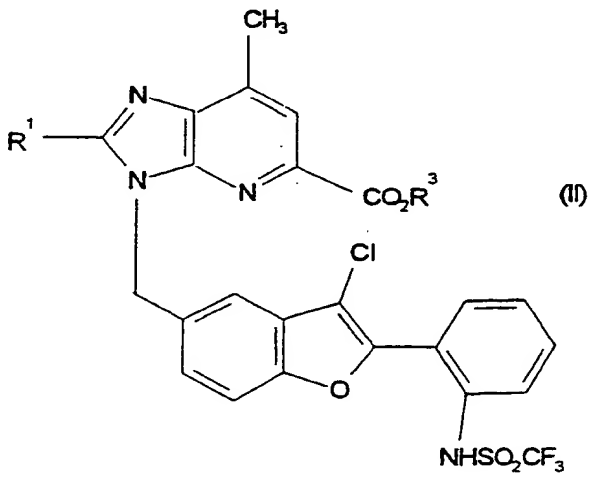
5. The compound

3-[[3-chloro-2-[2-[[(trifluoromethyl)sulphonyl]amino]phenyl]-5-benzofuranyl]methyl]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridine-5-methanol;
or a physiologically acceptable salt or solvate thereof.

6. The compound
N-[2-[3-chloro-5-[[5-[2-(hydroxypropyl)]-7-methyl-2-propyl-3H-imidazo[4,5-b]pyridin-3-yl]methyl]-2-benzofuranyl]phenyl]trifluoromethanesulphonamide;
or a physiologically acceptable salt or solvate thereof.

7. A process for the preparation of the compound as claimed in Claim 2 or a physiologically acceptable salt or solvate thereof which comprises reacting the compound 2-[3-chloro-5-[(5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridin-3-yl)methyl]-2-benzofuranyl]benzeneamine with trifluoromethanesulphonic anhydride or trifluoromethylsulphonyl chloride.

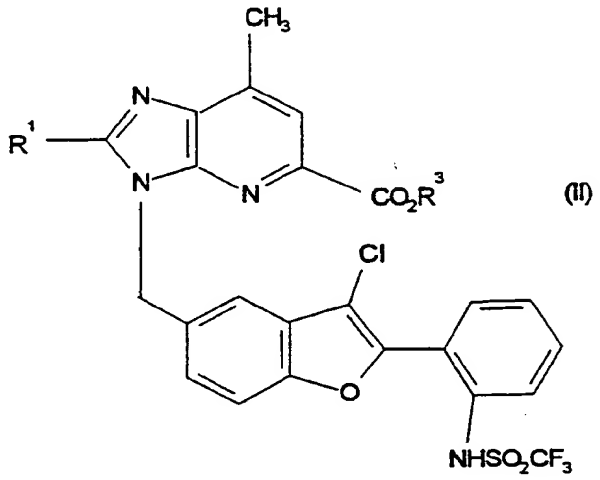
8. A process for the preparation of a compound as claimed in either Claim 3 or Claim 5 or a physiologically acceptable salt or solvate thereof which comprises reducing a compound of formula (II)



(II)

(wherein R^1 is ethyl or propyl and R^3 is a C_{1-4}alkyl group)
using a reducing agent.

9. A process for the preparation of a compound as claimed in either Claim 4 or Claim 6 or a physiologically acceptable salt or solvate thereof which comprises methylating a compound of formula (II)



(II)

(wherein R^1 is ethyl or propyl and R^3 is a C_{1-4}alkyl group) using a Grignard reagent, followed by hydrolysis.

10. A pharmaceutical composition comprising at least one compound as claimed in any one of Claims 1 to 6 or a physiologically acceptable salt or solvate thereof, together with at least one physiologically acceptable carrier or excipient.

11. A compound as claimed in any one of Claims 1 to 6 or a physiologically acceptable salt or solvate thereof for use in therapy, for example,

(i) for use in the treatment or prophylaxis of hypertension; or

(ii) for use in the treatment or prophylaxis of congestive heart failure, acute or chronic heart failure, aortic or cardiac insufficiency, post-myocardial infarction, renal insufficiency and renal failure (for example, as a result of diabetic nephropathy, glomerular nephritis, scleroderma or renal crisis), proteinuria, Bartter's syndrome, secondary hyperaldosteronism, Reynaud's syndrome, cerebrovascular insufficiency, peripheral vascular disease, diabetic retinopathy glaucoma, atherogenesis and for the improvement of vascular compliance; or

(iii) for use in the treatment or prophylaxis of cognitive disorders such as dementia (e.g. Alzheimer's disease) and other CNS disorders, such as anxiety

disorders, schizophrenia, depression and alcohol or drug (e.g. cocaine) dependency; or

(iv) for use in the treatment or prophylaxis of conditions associated with excessive or unregulated angiotensin II antagonist activity; or

(v) for use in the treatment or prophylaxis of a condition associated with activation of the Renin-Angiotensin System.

12. Use of a compound as claimed in any one of Claims 1 to 6 or a physiologically acceptable salt or solvate thereof the manufactuore of a therapeutic agent,

(i) for use in the treatment or prophylaxis of hypertension; or

(ii) for use in the treatment or prophylaxis of congestive heart failure, acute or chronic heart failure, aortic or cardiac insufficiency, post-myocardial infarction, renal insufficiency and renal failure (for example, as a result of diabetic nephropathy, glomerular nephritis, scleroderma or renal crisis), proteinuria, Bartter's syndrome, secondary hyperaldosteronism, Reynaud's syndrome, cerebrovascular insufficiency, peripheral vascular disease, diabetic retinopathy glaucoma, atherogenesis and for the improvement of vascular compliance; or

(iii) for use in the treatment or prophylaxis of cognitive disorders such as dementia (e.g. Alzheimer's disease) and other CNS disorders, such as anxiety disorders, schizophrenia, depression and alcohol or drug (e.g. cocaine) dependency; or

(iv) for use in the treatment or prophylaxis of conditions associated with excessive or unregulated angiotensin II antagonist activity; or

(v) for use in the treatment or prophylaxis of a condition associated with activation of the Renin-Angiotensin System.

13. A method for the treatment or prophylaxis of

(i) hypertension; or

(ii) congestive heart failure, acute or chronic heart failure, aortic or cardiac insufficiency, post-myocardial infarction, renal insufficiency and renal failure (for example, as a result of diabetic nephropathy, glomerular nephritis, scleroderma or renal crisis), proteinuria, Bartter's syndrome, secondary hyperaldosteronism, Reynaud's syndrome, cerebrovascular insufficiency, peripheral vascular disease,

diabetic retinopathy, glaucoma, atherogenesis and for the improvement of vascular compliance; or

(iii) cognitive disorders such as dementia (e.g. Alzheimer's disease) and other CNS disorders, such as anxiety disorders, schizophrenia, depression and alcohol or drug (e.g. cocaine) dependency; or

(iv) conditions associated with excessive or unregulated angiotensin II antagonist activity; or

(v) a condition associated with activation of the Ranin-angiotensin System,

which comprises administering an effective amount to a patient in need of such treatment, of a compound as claimed in any one of Claims 1 to 6 or a physiologically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/EP 93/03157

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D471/04 A61K31/435 //(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 434 249 (GLAXO) 26 January 1991 see claims 1,18,19	1,10,11
P,X	EP,A,0 514 197 (GLAXO) 19 November 1992 see claims 1,18,19	1,10,11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 February 1994	25. 02. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/EP 93/03157

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]al Application No
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